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Total macular volume as a potential biomarker in the assessment of anti-VEGF response in patients with diabetic macular edema: real-life data analysis

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ABSTRACT

Aim: To evaluate the functional and anatomic efficacy of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy in patients with diabetic macular edema (DME) and investigate the association between central macular thickness (CMT) and total macular volume (TMV) in real-life settings.

Material and Method: In this retrospective, observational, longitudinal study 38 eyes of 23 consecutive patients with center-involving DME were included. A loading phase of three monthly intravitreal anti-VEGF injections was initiated, followed by anti-VEGF injections if needed as per clinicians' discretion.

Results: Mean Early Treatment Diabetic Retinopathy Study (ETDRS) letters gained was 3.2 letters at month 12. The reduction in the mean of CMT and TMV were 60 μm and 1.33 mm^3 respectively at the end of 12 months. Best-corrected visual acuity (BCVA) was negatively correlated with CMT ($r=-0.573$, $p < 0.01$) and TMV ($r=-0.533$, $p < 0.01$) initially. There was a statistically significant positive correlation between the CMT and the TMV initially ($r=0.765$, $p < 0.01$) and month 12 ($r=0.937$, $p < 0.01$). Baseline TMV was found to be more predictive of treatment response at the 9th month than baseline CMT.

Conclusion: It is demonstrated that TMV may be a suitable biomarker in the assessment of treatment response of the macular region when regarded as a complete three-dimensional macular unit instead of central vertical thickness only. Although the present study contributes to a better understanding of managing DME in real-life settings, further prospective, and controlled investigations are needed.

Keywords: Aflibercept, anti-VEGF, central macular thickness, diabetic macular edema, total macular volume

INTRODUCTION

Diabetic macular edema (DME) is one of the most common ocular manifestations of diabetic retinopathy (DR). This pathology, which can be seen at any stage of DR (non-proliferative or proliferative), is also among the primary causes of vision loss (1). Although it is still not fully understood in all details, exudative fluid pooling in the intraretinal layers of the macula as a result of the blood-retinal barrier disruption is held responsible for the pathogenesis of DME (2). Also, with the emergence of the association between hypoxia-induced increased vascular endothelial growth factor (VEGF) and capillary leakage from retinal vessels in the pathogenesis; anti-VEGF treatment modalities have come into prominence plausibly.

Spectral-domain optical coherence tomography (SD-OCT) not only enables us to examine retinal structures layer by layer but also provides us with qualitative and quantitative information related to pathological alterations because of DME in the retina (3). SD-OCT has become a clinic of importance in diagnosis and classifying DME along with monitoring the treatment response (4). Previous studies showed that the assessment of central macular thickness (CMT) is a useful parameter for diagnostic sensitivity and quantitative monitoring in DME (2,3). Whereas CMT does not always accurately depict real numerical value owing to the differences in the retinal thickness of different sectors (5-7). Hence, we hypothesized that total macular volume (TMV), which can be neglected at times and offers an opportunity for a comprehensive approach, is of critical importance in clinical evaluation along with CMT.

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In clinical trials, highly determined patients are preferred to maintain timely attendance, or study criteria are strict in terms of glycemic controls, additional systemic disorders, age, etc. However, real-life settings, especially in the era of COVID-19 pandemics, may influence patient adherence and treatment response. The purpose of the current study was to investigate the association between CMT and TMV measured by SD-OCT and evaluate the functional and anatomic efficacy of intravitreal anti-VEGF therapy in patients with DME in real-life settings.

MATERIAL AND METHOD

This retrospective, observational, longitudinal study was conducted in a tertiary eye care referral center. This study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 2022, Decision No: E1-21-2179/2022). All procedures were carried out per the ethical rules and the principles of the Declaration of Helsinki. Informed written consent was obtained from all patients before receiving the anti-VEGF injections.

Study Population

Following the retrospective review of charts and intravitreal anti-VEGF logs (January 2020 - December 2021), 38 eyes of 23 consecutive patients with follow-up for at least 12 months with treatment naïve center-involving DME were included in the study. Although DME has the feature of showing bilateral involvement, it usually progresses asymmetrically. Therefore, macular findings in different eyes of the same case may be dissimilar (8, 9). That's why the second eye of some patients was also included in the study. Eighteen-year-old or older patients with severe nonproliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR), [determined by the modified Early Treatment Diabetic Retinopathy Study (ETDRS) grade] (10), at the first visit and met the following criteria were included in the study: Central subfield macular thickness of 250 μm or more on SD-OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany); absence of potential causes other than DME of decreased visual acuity. Patients who met the following criteria were excluded from the study: high refractive error (≥6 diopters), posterior staphyloma, prior intraocular operation other than cataract surgery, glaucoma, history of any retinal disease other than DR, images with low picture quality less than 16 dB due to corneal opacity, dens cataract, vitreous hemorrhage, etc.

A comprehensive ophthalmological examination including detailed medical history, best-corrected visual acuity (BCVA), non-contact tonometry, dilated fundoscopy, and SD-OCT was performed initially and on the following visits for all patients. Fluorescein angiograms were done at the baseline for each patient and then as needed. HbA1c level was reported at baseline. Visual acuity readings were converted from the Snellen chart to the logarithm of the minimal angle of resolution (log MAR) units and Early Treatment Diabetic Retinopathy Study (ETDRS) letters (11).

All eyes included in the study were initiated on a loading phase of three-monthly intravitreal bevacizumab injections in accordance with the respective regulations of the ministry of health, followed by aflibercept injections if needed as per clinicians' discretion with monthly monitoring for at least 12 months. An "as needed" or in other words pro re nata (PRN) regimen was employed that was shown to have caused a reduction in the number of injections while keeping a close follow-up plan for the treatment responses(12, 13). The same retina specialist examined each patient. The criteria for reinjection were at least one of the following: A decrease in BCVA; an increase in CMT; or both. While planning the treatment, the BCVA, CMT, and TMV of each eye were evaluated independently of the fellow eyes. In addition, the response of the anti-VEGF treatment for each eye was evaluated individually in the study. For standardization, only patients that received aflibercept as an anti-VEGF treatment after the obligatory loading phase of bevacizumab were included in the study. Based on the treatment response parameters of visual acuity and SD-OCT examination stability of the patients (if there was a possibility for additional enhancement), further intravitreal injection treatment decisions were made at subsequent visits.

The loading phase of injection was restarted in a total of 12 eyes of 7 patients who did not complete their loading phase of injections and did not attend their regular patient visits initially. One of the loading doses failed in these patients because of their nonadherence due to pandemics. So, they restarted receiving three-monthly loading doses. The inclusion of these patients did not cause any statistically significant difference in the statistical analysis.

Evaluation of Macular Thickness and Volume

Retinal thickness was computed as the length between the anterior retinal boundary of the internal limiting membrane and the posterior retinal boundary of the outer border of the retinal pigment epithelium. Retinal thickness assessment generated automatically includes a map analysis with measurements as defined by ETDRS (14) for each of the 9 subfields. The retinal thickness in a 1-mm diameter circle at the fovea was used for automated CMT measurements. CMT was calculated automatically with the built-in analysis software

of the SD-OCT. Along with this, automated TMV measurements were obtained in the 6x6-mm macular area centered on the fovea using the preprogrammed "fast macular volume" setting, containing a 25-line horizontal raster scan covering 20° × 20°, fixated on the fovea.

Statistical Analysis

Statistical analyses were performed with SPSS program version 26.0 (SPSS Inc., Chicago, Illinois, USA). Results were expressed as the mean±standard deviation. The Kolmogorov-Smirnov test was performed to determine whether the data were normally distributed. Upon the distribution of data was non-normally, Wilcoxon signed-rank test and Spearman's correlation coefficient were used. Also employed is a simple linear regression model which estimates the relationship between one independent variable and one dependent variable using a straight line. Differences with a P value less than 0.05 were considered statistically significant.

RESULTS

Demographics

Data for 38 eyes (22 right eyes, 16 left eyes) of 23 patients (11 women, 12 men; mean age 60.5±9.8 years) was analyzed. All participants were Caucasian. Only one patient had type I diabetes mellitus (DM) and 22 patients had type II DM. Six patients were on oral anti-diabetic medication, one patient was on insulin medication, and the remaining were on a combination of these treatments.

The mean duration of DM was 10.5 years (standard deviation [SD]±2.2). The mean chronic HbA1c level was 8.45±2.42% at enrollment. Twenty-five (66%) eyes had NPDR, and 13 (34%) eyes had PDR. One patient had renal insufficiency secondary to diabetic nephropathy that did not necessitate dialysis. Four patients were on medication for hypertension, which was well-controlled (**Table 1**).

The mean BCVA (standard deviation (SD); Snellen) was 71.3 (0.3; 0.53) ETDRS letters (min. 0.1 - max. 0.7 Snellen), CMT was 427.9±161.8 (min. 257 - max. 880) μm, and TMV was 10.6±2.4 (min. 7.82 - max. 15.28) mm^3 before the initiation of treatment. The mean BCVA (standard deviation (SD); Snellen) was 74.5 (0.2; 0.60) ETDRS letters (min. 0.1 - max. 1.0 Snellen), CMT was 367.6±132.1(min. 235 - max. 673) μm, and TMV was 9.3±2.2 (min. 6.25 - max. 14.46) mm^3 at month 12. The mean ETDRS letters gained was 3.2 ETDRS letters at month 12. The reduction in the mean of CMT and TMV were 60.3 μm and 1.3 mm^3 respectively at the end of 12 months (**Figure 1.**). The average of total intravitreal injections was 4.4 per eye at the end of 12 months.

Table 1. Initial clinical characteristics and demographic data of patients in this study

Age, years, mean±SD	60.5±9.8
Gender, female/male	11/12
Eyes, OD/OS	22/16
Duration of DM, years, mean±SD	10.5±2.2
DM type, type 1: type 2	2:36
Other systemic conditions	
Hypertension (blood pressure ‡ 140/90 mmHg)	4 (17.3%)
Nephropathy	2 (8.6%)
Sugar control	
Oral hypoglycemic agents	10 (26.3%)
Insulin	2 (5.3%)
Combination	26 (68.4%)
HbA1c level, %	8.4±2.4
Study eye, right: left eyes	22:16
Snellen Corrected visual acuity, mean±SD, (logMAR: ETDRS)	0.53±0.30 (0.27: 74)
Lens status	
Phakic Clear	37 (97.4%)
Pseudophakia	1 (2.6%)
Diabetic retinopathy grading	
Non-proliferative diabetic retinopathy	25 (65.8%)
Proliferative diabetic retinopathy	13 (34.2%)
OCT findings, mean±SD	
Central subfield thickness, μm	427.9±161.8
Total macular volume, mm^3	7.82±2.4

SD: standard deviation; OD: right eye; OS: left eye; DM: diabetes mellitus; logMAR=logarithm of the minimum angle of resolution; OCT: optical coherence tomography.

Correlations

BCVA at baseline was negatively correlated at moderate level with CMT initially (r=-0.573, $p < 0.01$) and month 3 (r=-0.510, $p < 0.01$). BCVA at baseline was negatively correlated at moderate level with TMV initially (r=-0.533, $p < 0.05$), month 3 (r=-0.580, $p < 0.01$) and month 6 (r=-0.576, $p < 0.01$) (**Table 2.**). There was a statistically significant positive correlation between the CMT and the TMV initially (r=0.765, $p < 0.01$) and month 12 (r=0.937, $p < 0.01$). Besides, the correlation of baseline CMT was stronger compared to baseline TMV for final BCVA (r=-0.437, $p < 0.05$).

Table 2. The Spearman's ranked correlation coefficient (Spearman's rho) for BCVA, CMT and TMV (n=38).

	Baseline BCVA	BCVA at 3rd month	BCVA at 6th month	BCVA at 9th month	BCVA at 12th month
Baseline CMT	-.573**	-.539**	-.527**	-.558**	-.437*
CMT at 3rd month	-.510**	-.302	-.452*	-.506**	-.524**
CMT at 6th month	-.343	-.333	-.313	-.434*	-.360
CMT at 9th month	-.122	.010	-.044	-.273	-.310
CMT at 12th month	-.005	.111	-.010	-.089	-.134
Baseline TMV	-.533*	-.465*	-.389	-.356	-.298
TMV at 3rd month	-.580**	-.423*	-.384	-.286	-.335
TMV at 6th month	-.576**	-.389	-.222	-.229	-.203
TMV at 9th month	-.355	-.106	.049	-.060	-.054
TMV at 12th month	-.338	-.042	-.185	-.113	-.150

BCVA: best-corrected visual acuity; CMT: central macular thickness; TMV: total macular volume. * $p < .05$. ** $p < .01$.

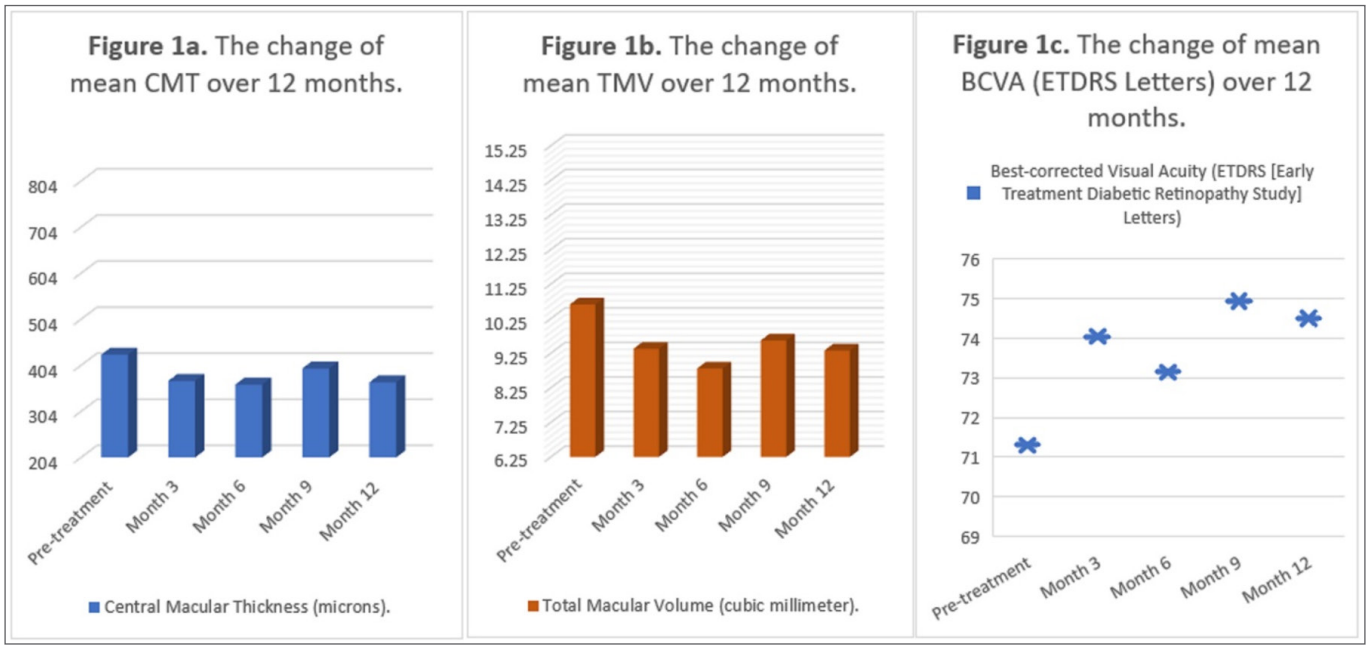

Figure 1. a. The change of mean central macular thickness (CMT) (microns) over 12 months. **b.** The change of mean total macular volume (TMV) (cubic millimeter) over 12 months. c. The change of mean best-corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letters over 12 months.

Regression Analysis

Given the results (**Table 3**a.), baseline CMT significantly predicted the CMT in the 9th month (R2=0.42; Freg=12.512, p<0.01). To be more precise, CMT at baseline explained 42% of the observed variance in patients' CMT at month nine. In view of the analysis (**Table 3**b.), baseline TMV significantly predicted the CMT in the 9th month (R2=0.52; Freg=13.366, p<0.01). More precisely, the baseline TMV explained 52% of the observed variance in patients' CMT at month nine. Baseline TMV was found to be more predictive of treatment response at the 9th month than baseline CMT.

Table 3a. Simple linear regression analysis results of baseline CMT related to predict of the CMT in the 9th month

Variables	B	SHB	Beta	t	R	R2	F
Constant	69.292	97.130		0.713	0.651	0.424	12.512
Baseline CMT	0.739	0.209	0.651	3.537			

Table 3b. Simple linear regression analysis results of baseline TMV related to predict of the CMT in the 9th month

Variables	B	SHB	Beta	t	R	R2	F
Constant	-79.819	133.371		-0.598	0.726	0.52	13,366
Baseline TMV	45.986	12.578	0.726	3.656			

CMT: central macular thickness; TMV: total macular volume; B: bias; SHB: sum of squares; Beta: beta coefficient; t: t statistic; R: the multiple correlation coefficient; R2: the coefficient of determination; F: F statistic.

According to the Wilcoxon signed-rank test for related samples results, there were significant differences in BCVA [z=-2.119, p<0.05], CMT [z=-2.059, p<0.05], and TMV [z=-2.417, p<0.05] between baseline and month 12. When the mean rank and sum of ranks of the difference scores were considered, this difference seemed in favor of the positive ranks, i. e., the month 12 scores.

DISCUSSION

DR is one of the major causes of considerable visual impairment in the population of employable age. DME, on the other hand, is the most common reason for vision loss in DR (15). Since the key role of VEGF has been proven in the pathogenesis of DME, intravitreal anti-VEGF injections were established as primary treatment for patients with DME. Multiple studies have demonstrated the improvement in both anatomical and functional outcomes secondary to anti-VEGF therapy for DME (15-17). With the increasing importance of objective and reproducible OCT imaging in the diagnosis and treatment of DME, qualitative and quantitative analyzes of structural characteristics in retinal layers have gathered momentum. In OCT imaging, CMT was acknowledged as a surrogate marker for assessing the treatment effect by several experts (18). Although CMT has been the most frequently utilized biomarker in DME, TMV may be more helpful, especially in non-center involved DME studies (7, 19). In addition, TMV may provide noteworthy data about the thickness of the macular region when regarded as a complete unit (19). In the current study, CMT and TMV were investigated and compared in terms of potential relation to anti-VEGF response in real-life settings.

Previous studies have shown anatomical and functional improvements in patients treated with intravitreal aflibercept injections for DME (16, 17, 20, 21). In the DRCR.net protocol T study, the mean letters gained after the treatment of aflibercept was approximately 10 ETDRS letters with an average of 9-10 injections per year (22). However, it was approximately 3.2 ETDRS letters with an

average of 4-5 injections per year in our study, which was a perspective on real-world evidence of anti-VEGF use in the COVID-19 era. These outcomes were significantly less than observed in the DRCR.net protocol T could be explained by reduced patient adherence and injection numbers. Plus, clinical trials were presented with a highly-motivated patient profile, strict criteria of the study, increased number of injections, and timely attendance. On the other side, there were numerous impediments such as restrictions due to the pandemics, the difficulty elderly patients have in getting an appointment, lack of capacity in hospitals, increased frequency of systemic comorbidities, and financial challenges in real-life settings.

In our study, anatomical enhancement was observed at the end of 12 months. There was a limited number of studies in the literature on TMV. In line with these limited previous studies, there was a decline in both CMT and TMV following intravitreal aflibercept treatments (15-17, 20-22). DRCR.net studies up to the present have demonstrated a high correlation of macular measurements with CMT. In the present study, while the correlation between baseline CMT and BCVA was statistically significant in the 3rd, 6th, 9th, and 12th months; the correlation between baseline TMV and BCVA was statistically significant only in the 3rd and 6th months. We thought that this may be caused by the reduced initial generalized macular edema after anti-VEGF treatment, which gave place to local (especially central) macular edema gradually later on. A regional variation such as central fovea, parafoveal and perifoveal area was possible in response to macular thickening secondary to treatment.

Browning et al. (7) concluded that TMV may be preferable over CMT when macular edema is more diffuse or when it is expected that responses of CMT may be inconsistent. In parallel with this, Panozzo et al. (19) suggested that considering the macular region as a whole may provide more significant information about retinal thickness, especially in cases with a stable measurement at the fixation point but an undetected global worsening. In a nonrandomized clinical trial, Nguyen et al. (23) found a significant decrease in TMV after anti-VEGF treatment. They proposed that the large effect of reduction in thickness of the central macula was accompanied by a global reduction in edema throughout the entire macula. Although time-domain OCT was used at the time of the mentioned works of literature published, current studies with spectral-domain OCTs also support the same argument(24-26). The therapeutical effect of anti-VEGFs' occurs in the retinal layers diffusely rather than focal lesions in the center of the fovea (27, 28). In conjunction with this, our simple linear regression analysis revealed that baseline TMV had higher predictability compared to baseline CMT for treatment response in the 9th month. However, it was not found statistically significant in the 12th month. It could be explained that diffuse edema might have decreased and become more localized in the 12th month. Besides, although CMT and TMV showed a regular decrease in the 3rd and 6th months, then a relatively gradual increase was observed in the 9th and 12th months. The decreased patient adherence after the completion of the three loading doses, which are obliged to be done regularly at least one month apart by regulations of the ministry of health could be the reason.

Study Limitations

Our study has several limitations. First, the sample size of treatment naïve patients was relatively small because of the COVID-19 pandemic. Second, quantitative metrics for further analysis such as intraretinal fluid or integrity of certain retinal layers were not available. The strength of this study includes the design of a real-life setting rather than a clinical trial setting which provides practical information for clinicians treating patients in the real world during the COVID-19 pandemic and the study group had a better homogeneity with the inclusion of only aflibercept-administered cases after the obligatory loading dose.

CONCLUSION

The current study demonstrated that baseline TMV might have higher predictability compared to baseline CMT for treatment response in patients with DME. Besides, TMV may be a suitable biomarker for the assessment of therapeutic effect in the macular region when regarded as a complete unit instead of central vertical thickness only. Utilizing TMV with CMT in the management of DME may provide a more consistent and comprehensive evaluation. Although the present study contributes to a better understanding of managing DME in real-life settings, further prospective, and controlled investigations are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 2022, Decision No: E1-21-2179/2022).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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